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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/553,656

10/14/2005

Ana Isabel Sanz Molinero

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EXAMINER

KUMAR, VINOD

ART UNIT

PAPER NUMBER

1638

MAIL DATE

DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/553,656	Applicant(s) SANZ MOLINERO, ANA ISABEL	
	Examiner VINOD KUMAR	Art Unit 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 February 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,4,6,7,9,10,25,27,28 and 30-34 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3,4,6,7,9,10,25,27,28 and 30-34 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 08 April 2008 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submissions filed on 12/22/08 and 2/25/09 have been entered.

Status of objections and rejections

2. Claims 1, 3-4, 6-7, 9-10, 25, 27-28 are 30-34 are pending.

Claims 2, 5, 8, 11-24, 26 and 29 are cancelled.

Accordingly, claims 1, 3-4, 6-7, 9-10, 25, 27-28 are 30-34 are examined on merits in the present Office action.

3. All claim objections made in the Office action of 6/20/08 are withdrawn in light of claim amendment filed in the paper of 12/22/08.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Rejection of claims 25, 27, 28, 30, 31 and 33-34 under 35 U.S. C. 102(b) is withdrawn in light of persuasive arguments filed in the paper of 12/22/08.

Claim Objections

6. Claims 1, 3-4, 6-7, 9-10, 25, 27-28 and 30-34 are objected to because of the following informalities:

Claim 1 is objected for lacking article before “Method” in line 1. It is suggested to change “Method” to --A method--.

Claim 1 is objected for having extra space between “protein” and “in” in line 3.

In claim 1, lines 3-4, it is suggested to change “increased expression in said plant of the nucleic acid” to --increased expression of the nucleic acid in said plant--.

Claims 3-4, 6-7 and 9 are objected for lacking article before “Method” in line 1. It is suggested to change “Method” to --The method--.

Claim 9 is objected for having improper article before “metallothionein” in line 2. It is suggested to change “a” to --said--.

Claim 10 is objected for having improper article before “method” in line 1. It is suggested to change “a” to --the--.

Claim 25 is objected for lacking article before “Method” in line 1. It is suggested to change “Method” to --A method--.

Claims 27-28 and 30-33 are objected for lacking article before “Method” in line 1. It is suggested to change “Method” to --The method--.

Claim 27 is objected for lacking punctuation mark at the end of the claim.

Claim 33 is objected for having improper article before “metallothionein” in line 2. It is suggested to change “a” to --said--.

Claim 34 is objected for having improper article before "method" in line 1. It is suggested to change "a" to --the--.

Appropriate action is requested.

Claim Rejections - 35 USC § 112

7. Claims 1, 3-4, 6-7, 9-10, 25, 27-28 and 30-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3, 25, 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in their recitations "genetic modification" which is confusing since the recitation reads on any genetic modification. It appears that is not the intent of the Applicant. It is suggested to change "a genetic modification as an indication of a plant with increased yield" in claims 1 and 25 to --said nucleic acid--. Likewise, it is suggested to change "said genetic modification" in claims 3 and 27 to --said nucleic acid--.

Dependent claims are also rejected because they fail to overcome the deficiency of parent claims 1 or 25.

Claim Rejections - 35 USC § 112

8. Claims 1, 3-4, 6-7, 9-10, 25, 27-28 and 30-34 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing plant seed yield comprising transformation of a plant with a nucleic acid

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sequence encoding a metallothionein protein as defined in SEQ ID NO: 2, does not reasonably provide enablement for (a) a nucleic acid sequence encoding any metallothionein protein or encoding any type 2 metallothionein protein, and (b) a nucleic acid sequence encoding a metallothionein protein having 95% identity to SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the reasons of record stated in the Office action mailed on 6/20/08. Applicant traverses the rejection in the paper filed on 12/22/08.

Applicant argues that one of ordinary skill will be able to make and use the claimed invention, without undue experimentation, from the teachings of the specification as well as the generally advanced level skill in the art. Applicant further argues that Type 2 metallothioneins are very well conserved and a person of ordinary skill in the art would readily recognize the effects of increased yield. Applicant further argues that SEQ ID NO: 2 comprises a conserved N-terminal domain typical of type 2 metallothioneins (response, paragraph bridging pages 5 and 6).

Applicant's arguments are fully considered but are deemed to be unpersuasive.

It is maintained that while the specification teaches a nucleotide sequence encoding SEQ ID NO: 2, it does not teach full scope of nucleotide sequences encoding other metallothionein protein that confer yield enhancement.

It is maintained that the state of art teaches that the precise function of metallothioneins remains to be elucidated. See for example, Robinson et al. (Biochem. J., 295:1-10, 1993; see in particular, page 1, left column, lines 8-30; page 5, table 1;

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page 8, last paragraph in right column through the end of 1st paragraph of page 9) who suggest that factors (stress and non-stress related) responsible for the induction of metallothionein gene expression vary significantly in the cells of different organisms, including plants, implying that members of metallothionein gene family are implicated in diverse cellular functions within the plant cell. Also see Chang et al. (Planta, 218:449-455, 2004; see in particular, abstract, page 449, right column; page 450, left column above materials and methods; page 452, figures 4-5; page 453, figures 6-7), who clearly suggest that class-2 metallothionein from sunflower might be involved in transport and availability of Cu^{2+} and Zn^{2+} to some apometal enzymes or apo-metal proteins.

Teachings of Robinson et al. or Chang et al. clearly suggest that not all metallothionein or type 2 metallothioneins would be expected to have similar biological role in a plant cell. Thus, it is maintained that one of skilled in the art would not expect all metallothioneins including class-2 metallothioneins to cause yield and/or growth enhancement to plants upon overexpression in a transgenic plant. The specification does not teach which metallothioneins or class-2 metallothioneins would confer this trait and which would not.

Applicant's attention is also drawn to page 7 (lines 2-3) of response filed 12/22/08, wherein Applicant states "The table below show comparative data using a type 1 (MT1) and a type 3 (MT3) metallothionein and show that an increase in seed yield (total weight of seeds) would not be obtained with all metallothioneins".

While the specification teaches a nucleotide sequences encoding SEQ ID NO: 2, it does not enable all nucleotide sequences encoding other metallothioneins or type 2 metallothioneins. Undue experimentation by one skilled in art would have been required to isolate other metallothioneins or type 2 metallothioneins from other sources and use them in increasing plant yield. See In re Bell, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993) and In re Deuel, 34 UPSQ2d, 1210 (Fed. Cir. 1995), which teach that the mere existence of a protein does not enable claims drawn to a nucleic acid encoding that protein. See also Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 at page 1027, where it is taught that the disclosure of a few gene sequences did not enable claims broadly drawn to any analog thereof.

In the absence of guidance, undue experimentation would have been required by one skilled artisan at the time the claimed invention was made to isolate other metallothioneins or class-2 metallothioneins from other sources and use them in a method of obtaining plant with increased growth/and or yield.

The instant specification fails to provide guidance on how to make nucleic acid sequences encoding a polypeptide having 95% sequence identity to SEQ ID NO: 2, and retaining the function of increasing plant yield upon expression of said nucleic acid sequence in a plant.

It is maintained that nucleic acid sequences having 95% sequence identity to the 81 amino acid long SEQ ID NO: 2 would encode proteins with 4 amino acid substitutions relative to SEQ ID NO: 2.

Making all possible single amino acid substitutions in an 81 amino acid long protein like that encoded by SEQ ID NO: 1 would require making and analyzing 19^{81} nucleic acid sequences; these proteins would have 98.7% identity to SEQ ID NO: 2.

Because nucleic acid sequences encoding proteins with 95% sequence identity to the 81 amino acid long SEQ ID NO: 2 which would encode proteins with 4 amino acid substitutions relative to SEQ ID NO: 2, many more than 19^{81} nucleic acid sequences would need to be made and analyzed.

It is maintained that the instant specification fails to provide guidance for which amino acids of SEQ ID NO: 2 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain biological activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme.

It is further maintained that making amino acid changes in SEQ ID NO: 2 protein is unpredictable. While it is known that many amino acid substitutions, additions or deletions are generally possible in any given protein the positions within the protein's sequence where such amino acid changes can be made with a reasonable expectation of success (without altering protein function) are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate

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only relatively conservative substitutions or no substitutions (see for example, Wells, Biochemistry 29:8509-8517, 1990, see pages 8511-8512, tables 1-2; Ngo et al., The Protein Folding Problem and Tertiary Structure Prediction, K. Merz., and S. Le Grand (eds.) pp. 492-495, 1994; see page 491, 1st paragraph).

It is thus maintained that making and analyzing proteins with unspecified changes in the amino acid sequence of SEQ ID NO: 2 that also have the biological activity of increasing seed yield would require undue experimentation.

Given the breadth of the claims, unpredictability of the art and lack of guidance of the specification, as discussed above, undue experimentation would have been required by one skilled in the art to make and use the claimed invention. Therefore, it is maintained that the claimed invention is not enabled as commensurate in scope with the claims.

9. Claims 1, 3-4, 6-7, 9-10, 25, 27-28 and 30-34 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record stated for the reasons of record stated in the Office actions mailed on 10/18/07 and 6/20/08. Applicant traverses the rejection in the paper filed on 12/22/08.

Applicant argues that page 7 of the specification provides consensus sequence of metallothionein proteins. Applicant further argues Figure 1 provides several examples of type 2 metallothioneins and their conserved regions (response, page 6, lines 9-15).

Applicant's arguments are carefully considered but are deemed to be unpersuasive.

The essential feature of the claims 1 and 32 is a nucleic acid sequence encoding a metallothionein protein which has 95% sequence identity to instant SEQ ID NO: 2.

The essential feature of claim 25 is any metallothionein protein from any source.

The essential feature of claims 6 and 30 is any type 2 metallothionein from any source.

While the specification describes increased seed yield function of SEQ ID NO: 2 when expressed in a transgenic plant (See pages 30-35, Examples 1-5; Table 2; Figures 2 and 30, however, the specification does not describe the structure for the full scope of metallothioneins including type 2 metallothioneins isolated from diverse sources. The specification does not describe the function of metallothioneins including type 2 metallothionein from diverse sources. The specification does not describe structure of sequences having 95% sequence identity to instant SEQ ID NO: 2.

It is maintained that there is no description of the structure required for the recited function, and no description of the necessary and sufficient elements of a metallothionein including type 2 metallothionein. Teachings of Robinson et al. or Chang et al. clearly suggest that not all metallothionein or type 2 metallothioneins would be

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expected to have similar biological role in a plant cell as discussed above. One of skilled in the art would not have reliably predicted to function of increased seed yield for the genus of sequences comprising metallothioneins and sequences 95% identical to SEQ ID NO: 2. Applicant's attention is also drawn to page 7 (lines 2-3) of response filed 12/22/08, wherein Applicant states "The table below show comparative data using a type 1 (MT1) and a type 3 (MT3) metallothionein and show that an increase in seed yield (total weight of seeds) would not be obtained with all metallothioneins".

Thus, Applicant's broadly claimed genus encompasses structures whose function is unrelated to the instantly claimed SEQ ID NO: 2. The specification fails to describe the function of increased seed yield or increased biomass for said structures.

The only species described in the specification is SEQ ID NO: 1, which encodes SEQ ID NO: 2. Nucleic acid sequences encoding metallothioneins including type 2 metallothioneins from diverse sources are not described, and thus their function is not known. Nucleic acid sequences encoding metallothioneins having 95% identity are not described, and thus their function is unknown.

It is therefore maintained that one of skill in the art would not recognize that Applicant was in possession of the necessary common attributes or features of the genus in view of the disclosed species. Since the disclosure fails to describe the common attributes that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 1 and 2 are insufficient to describe the claimed genus.

There is no description of the structure required for the recited function, and no description of the necessary and sufficient elements of a metallothionein protein of SEQ ID NO: 2.

One of skill in the art would not recognize that Applicant was in possession of the necessary common attributes or features of the genus in view of the disclosed species. Since the disclosure fails to describe the common attributes that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 1 and 2 are insufficient to describe the claimed genus.

Therefore, given the lack of written description in the specification with regard to the structural and functional characteristics of the claimed compositions, it is not clear that Applicant was in possession of the claimed genus at the time this application was filed.

Accordingly, there is lack of adequate description to inform a skilled artisan that applicant was in possession of the claimed invention at the time of filing. See Written Description guidelines published in Federal Register/Vol.66, No. 4/Friday, January 5, 2001/Notices; p. 1099-1111.

Also see *in re Curtis* (69 USPQ2d 1274 (Fed. Cir.2004)), where the court held that there was sufficient evidence to indicate that one of ordinary skill in the art could not predict the operability of other species other than the single one disclosed in the specification. The court held that a disclosure naming a single species can support a claim to a genus that includes that species if a person of ordinary skill in the art, reading the initial disclosure, would “instantly recall” additional species of the genus already

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“stored” in the minds, but if other members of the genus would not “naturally occur” to a person of ordinary skill upon reading the disclosure, then unpredictability in performance of species other than specifically enumerated defeats claims to the genus.

For at least these reasons and the reasons of record stated in the previous Office Action, the requirement for written description has not been met. Accordingly, the rejection is maintained.

Claim Rejections - 35 USC § 103

10. Claims 1, 3-4, 6-7, 9-10, 25, 27-28 are 30-34 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Basel et al. (WIPO Publication No. WO 98/36084, Published 20 August, 1998, Applicant's IDS) in view of Zhou et al. (Mol. Gen. Genet. 248:318-328, 1995) for the reasons of record stated in the Office action mailed on 6/20/08. Applicant traverses the rejection in the paper filed on 12/22/08.

Applicant argues that increase in growth rate does not automatically result in an increase in yield. Applicant further argues that depending on the plant in question, an increase in the number or girth of the stems may constitute increased yield, whilst for others an increase in leaf, tuber or seed size or number that constitutes an increase in yield (response, paragraph bridging pages 7 and 8).

Applicant's arguments are carefully considered but are deemed to be unpersuasive.

It is maintained that Basel et al. teach a method of making a transgenic plant with increased growth and development comprising introducing and overexpressing a

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nucleic acid sequence encoding a metallothionein, and wherein the nucleic acid is expressed under a constitutive promoter. See in particular, pages 2, lines 11-23; page 9, lines 7-14; page 35, line 6; page 37, line 12; SEQ ID NO: 7.

It is also maintained that Zhou et al. teach a nucleic acid sequence encoding *Arabidopsis* type 2 metallothionein protein (MT2a) which has 100% sequence identity to instant SEQ ID NO: 2. The reference further teaches that nucleic acid sequences encoding members of metallothionein proteins are differentially regulated. In particular, MT2a is overexpressed in the mature leaves and inflorescence, compared to other members of the gene family. See in particular, page 318, abstract; page 322, figure 3; page 324, figures 6 and 7; page 326, 2nd column through the end of 1st column of page 327.

It is therefore, maintained that it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of making a transgenic plant with increased growth and development as taught by Basel et al., to substitute the coding sequence encoding Basel et al. metallothionein protein with a nucleotide sequence encoding Zhou et al. type 2 metallothionein protein to obtain a transgenic plant and transgenic seed expressing Zhou et al. metallothionein protein.

Given that Basel et al. teach that overexpressing a metallothionein protein in a plant improves growth and development and Zhou et al. teach that type 2 metallothionein proteins (MT2a, in particular) are highly expressed in tissues like leaf and inflorescence, it would have been obvious and within the scope of an ordinary skill in the art to have been motivated to express Zhou et al. sequence in a plant to obtain

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transgenic plants having improved growth and development with a reasonable expectation of success. It would have been obvious that increased growth and development would have improved yield, such as seed yield with a reasonable expectation of success.

It is important to note that it would have been obvious that one of ordinary skilled in the art would have also observed increased seed yield in the transgenic plants overexpressing Zhou et al. type 2 metallothionein protein because increased seed yield trait is due to the expression of instant SEQ ID NO: 2 which has 100% identity to Zhou et al. type 2 metallothionein protein. Thus, while one of ordinary skill in the art would have expressed Zhou et al. type 2 protein in a plant using any method of plant transformation including the one taught by Basel et al. for the purpose of obtaining a transgenic plant with improved growth and development, it would have been obvious that said plant would have also exhibited any other characteristics including increased seed yield trait that is directly related to the property of Zhou et al. protein over-expression in said transgenic plants with a reasonable expectation of success.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have

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been obvious and within the scope of an ordinary skill in the art to combine the teachings of Basel et al. and Zhou et al. to arrive at the claimed invention with a reasonable expectation of success.

Thus, it is maintained that the claimed invention as a whole is prima facie obvious over the combined teachings of the prior art.

Conclusions

11. Claims 1, 3-4, 6-7, 9-10, 25, 27-28 are 30-34 remain rejected.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vinod Kumar whose telephone number is (571) 272-4445. The examiner can normally be reached on 8.30 a.m. to 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vinod Kumar/

Examiner, Art Unit 1638